Adjuvant interferon for the treatment of high-risk melanoma: an individual patient data meta-analysis

Ives, Natalie; Wheatley, Keith; Suciu, Stefan; Eggermont, Alexander M.; Kirkwood, John M.; Lorigan, Paul; Markovic, Svetomir; Garbe, Claus

DOI:
10.1016/j.ejca.2017.06.006

Document Version
Peer reviewed version

Citation for published version (Harvard):
Ives, N, Wheatley, K, Suciu, S, Eggermont, AM, Kirkwood, JM, Lorigan, P, Markovic, S & Garbe, C 2017, 'Adjuvant interferon for the treatment of high-risk melanoma: an individual patient data meta-analysis', *European Journal of Cancer*, vol. 82, pp. 171-183. https://doi.org/10.1016/j.ejca.2017.06.006

Adjuvant interferon-α for the treatment of high-risk melanoma: an individual patient data meta-analysis

Natalie J. Ives[a] MSc, Stefan Suciu[b] PhD, Alexander MM. Eggermont[c] MD, John Kirkwood[d] MD, Paul Lorigan[e] MD, Svetomir N. Markovic[f] MD, Claus Garbe[g] MD, Keith Wheatley[h] PhD: on behalf of the International Melanoma Meta-Analysis Collaborative Group (IMMCG)

[a] Birmingham Clinical Trials Unit, College of Medical and Dental Sciences, Public Health Building, University of Birmingham, Edgbaston, B15 2TT, United Kingdom

[b] EORTC Headquarters, Avenue Emmanuel Mounier 83/11, 1200 Brussels, Belgium

[c] Gustave Roussy Cancer Campus Grand Paris, 114 Rue Edouard Vaillant, 94800, Villejuif, France

[d] University of Pittsburgh Cancer Institute and School of Medicine, 5117 Centre Avenue, Pittsburgh, PA 15213, United States of America

[e] The Christie NHS Foundation Trust, 550 Wilmslow Road, Manchester, M20 4BX, United Kingdom

[f] Mayo Clinic Rochester, 200 First St. SW, Rochester, MN 55905, United States of America

[g] University of Tubingen, Liebermeisterstraße 25, 72076 Tübingen, Germany

[h] Cancer Research UK Clinical Trials Unit, College of Medical and Dental Sciences, Robert Aitken Institute, University of Birmingham, Edgbaston, B15 2TT, United Kingdom

Corresponding author:

Professor Keith Wheatley, Cancer Research UK Clinical Trials Unit, College of Medical and Dental Sciences, Robert Aitken Institute, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK.
Tel: +44 (0) 121 415 9119
E-mail: k.wheatley@bham.ac.uk

Sources of Support

No funders were directly involved in the project. This work was supported by the University of Birmingham Clinical Trials Unit who received core support from the UK Department of Health, through the National Co-ordinating Centre for Research Capacity Development, up to March 2012, which funded Natalie Ives. A core grant from the Fonds Cancer, FOCA (BE), provides support for the EORTC Headquarters staff (co-author, Stefan Suciu).

Word Count: 2889

Abstract

Background

Many randomised trials assessing interferon-α (IFN-α) as adjuvant therapy for high-risk malignant melanoma have been undertaken. To better assess the role of IFN-α, an individual patient data (IPD) meta-analysis of these trials was undertaken.

Methods

IPD was sought from all randomised trials of adjuvant IFN-α versus no IFN-α for high-risk melanoma. Primary outcomes were event-free survival (EFS) and overall survival (OS). Standard methods for quantitative IPD meta-analysis were used. Subgroup analyses by dose, duration of treatment, and various patient and disease-specific parameters were performed.

Findings

Fifteen trials were included in the analysis (eleven with IPD). EFS was significantly improved with IFN-α (Hazard Ratio (HR)=0·86, CI 0·81-0·91; P<0·00001), as was OS (HR=0·90, CI 0·85-0·97; P=0·003). The absolute differences in EFS at five and ten years were 3·5% and 2·7%, and for OS were 3·0% and 2·8% respectively in favour of IFN-α. There was no evidence that the benefit of IFN-α differed depending on dose or duration of treatment, or by age, gender, site of primary tumour, disease stage, Breslow thickness, or presence of clinical nodes. Only for ulceration was there evidence of an interaction (test for heterogeneity: P=0·04 for EFS; P=0·002 for OS); only patients with ulcerated tumours appeared to obtain benefit from IFN-α.

Conclusion

This meta-analysis provides clear evidence that adjuvant IFN-α significantly reduces the risk of relapse and improves survival, and shows no benefit for higher doses. The

increased benefit in patients with ulcerated tumours, and lack of benefit in patients without ulceration, needs further investigation.

Key Words: Individual patient data meta-analysis; randomised controlled trials; melanoma; adjuvant interferon.

Introduction

Effective adjuvant therapy for melanoma remains an unmet need. Despite the approval of two new agents (Ipilimumab, PEGylated interferon (PEG-IFN)), the last five years have not seen improvements in overall survival (OS) in any adjuvant therapy study. Interferon remains a standard of care in many countries without a consensus view on its clinical utility. Results from randomised trials of adjuvant interferon-α (IFN-α) in high-risk melanoma have been considered inconsistent, with some suggesting benefit with IFN-α and others showing no difference.[1] In 1996, high dose IFN-α was approved in both the US and Europe based on the results of the ECOG 1684 trial in stage IIB/III patients, which showed a benefit for high dose IFN-α on both relapse-free survival (RFS) and OS.[2] Updated results with a median follow-up of 12·6 years, showed that the RFS benefit was maintained (Hazard Ratio (HR)=0·72, p=0·02), but the HR for OS had decreased from 0·67 to 0·82 (p=0·18), possibly due to competing causes of death.[3] The ECOG E1690 trial which compared high and low dose IFN-α versus observation also in stage IIB/III patients, had a very similar outcome for RFS for high and low dose, but did not confirm the benefit for high or low dose on OS.[4]

In Europe, low dose IFN-α was also approved based on a French trial in stage II patients, which showed a RFS benefit (HR=0·75, p=0·035), and a trend towards improved OS (HR=0·72, p=0·059).[5] In 2011, the US Food and Drug Administration (FDA) approved PEG-IFN for stage III melanoma based on the EORTC 18991 trial, which showed an event-free survival (EFS) benefit (HR=0·82, p=0·01), but again no OS benefit.[6]

Previous meta-analyses of the interferon trials have shown that IFN-α has a consistent effect on RFS, but no clear effect on OS.[7-9] No relationship with dose or duration of

treatment with outcome has been demonstrated.[7,8] IFN-α can have substantial side-effects, especially at high doses. Obtaining a reliable estimate of the true benefit of IFN-α, and determining whether the magnitude of the benefit differs in different treatment regimens or disease characteristics is important. To this end, we have performed an individual patient data (IPD) meta-analysis of randomised trials of IFN-α versus no IFN-α in patients with high-risk melanoma.

Methods

Trial Identification

Randomised trials comparing IFN-α with no IFN-α in the adjuvant setting for the treatment of high-risk melanoma were identified by searches of registers and electronic databases including the Cochrane Controlled Trials Register, MEDLINE, EMBASE, PubMed, and Web of Science. This was supplemented by searching abstract books of conference proceedings from the main meetings (e.g. American Society of Clinical Oncology, World Melanoma Congress, ESMO/ECCO), scanning reference lists of retrieved papers, and contact with individual trialists. Trials of IFN-α versus other agents or involving vaccines were not considered for the primary analysis.

Data Collection

IPD was requested from all trials eligible for inclusion in the meta-analysis. For each patient, information was sought on age, gender, site of primary tumour, disease stage (American Joint Committee on Cancer (AJCC) staging system for cutaneous melanoma preferred [10]), Breslow thickness, ulceration, clinical nodes, and metastatic status. Data on allocated treatment, date of randomisation, date and site of first recurrence, date of first distant recurrence, and date and cause of death was also collected. All data were checked for internal consistency, and were amended or updated as necessary through correspondence with the responsible investigators.

Statistical Analysis

Standard meta-analytic methods were used to estimate an overall treatment effect for IFN-α versus no IFN-α (control) patients.[11-13] All analyses were based on the intention-to-treat principle. To summarise, the number of events observed (O) in the IFN-α group of

each trial was compared with the number of events that would have been expected (E) if there was no difference between the IFN-α and control groups. The difference between these numbers, the observed minus expected (O-E), and its variance, yields the log-rank test for each trial. For trials providing IPD, each trial was analysed separately, and the log-rank statistics were used to calculate that trial's O-E and variance.[12] For trials where IPD was not provided, log-rank data was extracted from the publications, and the O-E and variance calculated using the methods described by Parmar.[13] From this O-E and variance, the HR and 99% confidence interval (CI) for each trial was calculated. Summing the statistics for each trial provides the overall statistics, which are presented as HR with 95% CI.[12,13]

For three-arm trials, treatment effects were estimated separately for each dose or duration of IFN-α versus control, but the control groups contribute only once to the totals (and relevant subtotals), with the statistics in the totals (and subtotals) being based on a single comparison of IFN-α (at either dose or duration) with no IFN-α.

The results are presented as forest plots and survival curves. In the former, the HR and 99% CI for each trial is represented graphically as a box with a line through it. The trials with IPD are shown as black boxes, and those trials with published data only are shown as white boxes. The overall results (and subtotals) are represented by diamonds, with the centre of the diamond giving the HR for the overall treatment effect and the width of the diamond the 95% CI. Only trials providing IPD contribute to the survival curves and subgroup analyses.

Outcome Measures

The primary outcomes were EFS (time from randomisation to first event, either recurrence or death without recurrence) and OS (time from randomisation to death). Secondary outcomes were time to disease recurrence (or recurrence-free survival), time to first distant recurrence, and time to death without recurrence.

These outcomes were analysed for all trials for which data were available. In the primary analysis, trials were divided by dose of IFN-α: high (20MU/m^2), intermediate (5 or 10MU), low (3MU), and very low dose (1MU). The EORTC 18991 trial of PEG-IFN was placed in its own subgroup beneath the high dose trials on the forest plots, as although this trial was thought to provide a similar IFN dose to that of the high dose trials, PEG-IFN may have different properties to standard IFN-α. Differences in treatment effects between trials and subgroups of trials were assessed using tests of heterogeneity or tests for trend. For the primary analysis by IFN-α dose, the tests for trend excluded the EORTC 18991 study.

Analyses were also performed with trials divided by duration of treatment (≤6, 12-18 and ≥24 months) and by total scheduled dose (<250MU, 500-1000MU, 1300-3400MU and ≥3500MU). For trials that provided IPD, the effect of IFN-α was also investigated by patient age (<40, 40-49, 50-59 and ≥60 years) and gender, and by different disease characteristics (site of primary tumour (limb or not limb), disease stage (stage I/II or stage III/IV as per definition used in each trial), Breslow thickness (≤1mm, 1.01-2.5mm, 2.51-4mm or >4mm), ulceration (no, yes or unknown), and clinical node (node negative (N-), node positive (N+)). When interpreting the results of these subgroup analyses, emphasis should be placed on the relevant tests for heterogeneity between subgroups (or test for

trend if the subgroup levels are ordinal, e.g. age), and not on the p-values for each stratum within the subgroup.

This IPD meta-analysis adheres to the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of individual participant data.[14]

Results

Fifteen randomised trials of IFN-α versus no IFN-α (control) were identified (Table 1, Supplemental Material Figure 1 and Supplemental Material Table 1).[2,4-6,15-24] There were three 3-arm studies comparing different doses or schedules of IFN-α with control, meaning there was 18 comparisons included in the analysis; ECOG 1690 trial [4] contributes to both the high and low dose IFN-α versus control subgroups, and the EORTC 18952 [15] and Nordic [18] trials each contribute two separate comparisons within the intermediate dose group. IPD was provided for 11 of the 15 trials (Supplemental Material Table 2); summary data was used for the Nordic, Austrian MMCG, French CGM and Sunbelt trials.

The 15 trials randomised 7744 patients (7699 patients analysed); the 11 trials providing IPD accounting for 5861 (76%) randomised patients. The mean age was 49 years (range: 14 to 85), 57% were male, 61% were in disease stage III, mean Breslow thickness was 3.8mm, 41% were clinical node positive, and 25% had ulcerated tumours (from 11 trials providing IPD; Supplemental Material Table 3). The duration of follow-up ranged from a mean of 3·4 years in the Austrian study (published data) to a median of 16·9 years in ECOG 1684 (IPD).

Event-free survival

Data on EFS were available for 7697 patients, with 4739 events reported. A significant improvement in EFS was seen with IFN-α compared with no IFN-α (HR=0·86, CI 0·81-0·91; P<0·00001) (Figure 1). In the 11 trials providing IPD, the estimated HR was 0·88 (CI 0·83-0·94; P=0·0003). This translated into absolute increases in five and ten year EFS of 3·5% and 2·7% respectively in favour of IFN-α (Figure 2). There was no evidence of any

trend depending on the dose: high (0·83, 0·72-0·96); intermediate (0·84, 0·74-0·95); low (0·85, 0·77-0·94), and very low dose (0·99, 0·80-1·23) (test for trend: P=0·3) (Figure 1). There was also no evidence of any trend depending on the duration of treatment (P=0·7) (Supplemental Material Figure 2) or total planned dose (P=0·6) (Supplemental Material Figure 3).

Overall Survival

Survival data were available for all patients (n=7699), with 3899 deaths observed. There was a significant improvement in OS with IFN-α compared with no IFN-α (HR=0·90, CI 0·85-0·97; P=0·003) (Figure 3). In the 11 trials providing IPD, the estimated HR was 0·91 (CI 0·85-0·98, P=0·01). This translated into absolute increases in five and ten year OS of 3·0% and 2·8% respectively in favour of IFN-α (Figure 4). There was no evidence of any trend depending on the dose: high (0·93, 0·80-1·08); intermediate (0·91, 0·79-1·04); low (0·86, 0·77-0·96), and very low dose (0·96, 0·76-1·21) (P=0·7) (Figure 3); duration of treatment (P=0·9) (Supplemental Material Figure 4); or total planned dose (P=0·4) (Supplemental Material Figure 5).

Recurrence-free survival

Recurrence-free survival was only available for the 11 trials providing IPD, with 3706 recurrences among 5826 patients. The result was similar to that for EFS. There was a significant improvement in recurrence-free survival with IFN-α (HR=0·88, CI 0·83-0·95; P=0·0004), with no difference in the effect of IFN-α between the four dose groups (P=0·1).

Distant Recurrence

Data on distant recurrence was only provided for 5 trials (WHO-16, DKG 80-1 and EORTC 18952, 18871 and 18991). There was no difference in the risk of distant recurrence between IFN-α and no IFN-α (HR=0·94, CI 0·85-1·03; P=0·2), with no difference in the effect of IFN-α between doses (P=0·3) (Supplemental Material Figure 6).

Death without Recurrence

Death without recurrence was only available for the 11 trials providing IPD. There were few cases of patients dying before disease recurrence (138 in 5826 patients), with no evidence of a difference between treatment groups (HR=0·87, CI 0·62-1·23; P=0·4). There was no difference in the effect of IFN-α between the four dose groups (P=0·09).

Subgroup Analyses by Patient and Disease Characteristics

There was no clear evidence that the effect of IFN-α differed for either EFS or OS for most of the pre-specified subgroups (Figure 5, Supplemental Material Figure 7). Only for ulceration was there evidence of a difference. In patients with ulcerated tumours, a significant improvement in EFS was seen with IFN-α versus control (HR=0·79, CI 0·66-0·94), compared to no difference in EFS in those with non-ulcerated tumours (HR=0·95, CI 0·82-1·10) (test for interaction: P=0·04) (Figure 5). A similar result was observed for OS; with improved survival for IFN-α versus control for patients with ulcerated tumours (HR=0·77, CI 0·64-0·92), but no difference in survival for patients with non-ulcerated tumours (HR=1·02, CI 0·87-1·20) (test for interaction: P=0·002) (Supplemental Material Figure 7). For ulcerated melanoma, the absolute difference at ten years in EFS and OS was 6·9% and 10.5% respectively in favour of IFN-α (Supplemental Material Figure 8).

Vaccine Trials (ECOG 1694 and 2696)

The primary analysis was an un-confounded comparison of IFN-α versus no IFN-α. There are also two vaccine trials: ECOG 1694 [25] comparing high dose IFN-α with GMK vaccine, and ECOG 2696 [26] (three-arm) comparing GM2-KLH/QS-21 vaccine with high dose IFN-α started either immediately (on day 0) or delayed (start on day 14) with GM2-KLH/QS-21 vaccine alone (Table 1, Supplemental Table 1). An analysis including the IPD from these trials gave the same results as the primary analysis (EFS: HR=0·86, CI 0·81-0·90; OS: HR=0·90, CI 0·85-0·96).

Discussion

This IPD meta-analysis brings together all the currently available data from randomised trials of adjuvant IFN-α versus no IFN-α for the treatment of high-risk malignant melanoma, providing the most reliable assessment to date on the role of IFN-α.

We have showed that IFN-α produces a clear benefit in terms of reducing the risk of recurrence, with a smaller benefit on OS. There was a highly significant 14% proportional reduction in the risk of an event (recurrence or death without recurrence) with IFN-α, similar to the 17% reduction observed in the published data meta-analysis of some of these trials reported previously.[7] In our published data meta-analysis, no significant benefit in OS was seen (7·3% reduction, P=0·1).[7] However, in this IPD meta-analysis, we found a significant 10% proportional reduction in the risk of death with IFN-α. Such a reduction might be clinically meaningful, although the absolute difference in mortality at 10 years was small (approximately 3%).

By collecting IPD, we were also able to assess the effect of IFN-α on recurrence-free survival, distant recurrence and death without recurrence. Data on distant recurrence was limited, though the effect size was consistent with that for EFS and recurrence-free survival. There were very few deaths without recurrence, with no difference between IFN-α and control.

The analyses presented here provide no evidence of a dose response relationship with the results for both EFS and OS being similar across the four doses of IFN-α (high, intermediate, low and very low). There was also no evidence that the results differed by

duration of treatment or total scheduled dose of IFN-α. This is an important finding, as high dose IFN-α is associated with significant toxicity and cost.

One of the main benefits of undertaking an IPD meta-analysis is that it allows the investigation of whether the treatment effect differs in different types of patients. We found no evidence to suggest that the effect of IFN-α differed with age, gender, site of primary tumour, Breslow thickness, disease stage, or presence of clinical nodes. Only for ulceration was there evidence of a difference, with those patients with an ulcerated tumour treated with IFN-α having greater benefits in both EFS and OS than patients with non-ulcerated tumours.

The ulceration finding was first reported in an earlier iteration of this IPD meta-analysis.[8] Wheatley et al. reported that patients with ulcerated tumours had greater benefit from IFN-α (EFS: HR=0·76, OS: HR=0·77) than those with no ulceration (EFS: HR=0·94, OS: HR=0·98).[8] In this updated analysis, the effect sizes are similar to those reported previously, but there is stronger evidence of a difference in benefit with IFN-α for ulcerated versus non-ulcerated tumours for OS. In an analysis of the two adjuvant EORTC IFN/PEG-IFN trials, tumour load in the lymph nodes and ulceration of the primary tumour came out to be independent predictive factors for adjuvant IFN-α therapy.[27] However, these two EORTC trials were included in the meta-analysis, so this analysis does not provide independent validation. While we cannot yet prove that IFN only works in patients with ulcerated primary tumours, the possibility of a larger, and hence more clinically worthwhile, benefit in these patients – with a corresponding lack of benefit in non-ulcerated patients – could allow more efficient targeting of this agent to patients who may benefit, while avoiding it – along with the associated toxicity – in patients unlikely to benefit.

Recently major advances in patients with advanced disease have been obtained with checkpoint inhibitors and with BRAF and MEK inhibitors.[28] Many of these agents are now being evaluated in the adjuvant setting. The control arm in these studies include placebo, high dose IFN and ipilimumab, highlighting the continuing lack of consensus agreement on what constitutes standard of care in the adjuvant setting. Adjuvant therapy with ipilimumab was approved by the FDA in 2015 on the basis of the results of the EORTC 18071 trial in stage III patients with high-risk for relapse, showing a significant improvement on event-free survival.[29]

The limitations of this review include publication bias, a potential problem for any meta-analysis. We had IPD for 11 of the 15 trials included in the meta-analysis; for the remaining four trials, published data was included. In these four trials, a slightly larger benefit for IFN-α was observed (EFS: HR=0·77, OS: HR=0·87). However, since IPD made up 76% of the data in this meta-analysis, the more positive results from the trials where only published data were available will not have greatly altered the results and their interpretation. Further, there was no clear evidence of a difference in the results between the trials with IPD and published data (P=0·07 for EFS; P=0·6 for OS).

This meta-analysis of trials of adjuvant IFN-α for high-risk melanoma provides clear statistical evidence of benefit on EFS and, to a lesser extent, on OS, but the absolute differences are relatively small. The finding that ulceration may be predictive of response to IFN-α is an important finding, and needs confirmation in prospective studies, such as the EORTC 18081 trial in stage II melanoma.

Conflict of Interest Statements:

NI, SS, SM and KW have nothing to disclose.

AE has received personal fees from BMS and MSD for sitting on Scientific Advisory Boards.

JK has received personal fees from Amgen, BMS, Genentech, Green Peptide and Roche and grants from Prometheus.

PL has received personal fees from Amgen, BMS, Chugai, GSK, Merck, Novartis and Roche for sitting on Scientific Advisory Boards and to support travel to meetings.

CG has received grants and personal fees from BMS, Novartis and Roche, and personal fees from Amgen, LEO and MSD for sitting on Scientific Advisory Boards and giving presentations.

References

[1] Lens MB, Dawes M. Interferon alfa therapy for malignant melanoma: a systematic review of randomized controlled trials. J Clin Oncol 2002;20:1818-25.

[2] Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. J Clin Oncol 1996;14:7-17.

[3] Kirkwood JM, Manola J, Ibrahim J, Sondak V, Ernstoff MS, Rao U; Eastern Cooperative Oncology Group. A pooled analysis of Eastern Cooperative Oncology Group and Intergroup trials of adjuvant high-dose interferon for melanoma. Clin Cancer Res 2004;10:1670-7.

[4] Kirkwood JM, Ibrahim JG, Sondak VK, Richards J, Flaherty LE, Ernstoff MS, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. J Clin Oncol 2000;18:2444-58.

[5] Grob JJ, Dreno B, de la Salmoniere P, Delaunay M, Cupissol D, Guillot B, et al. Randomised trial of interferon alpha-2a as adjuvant therapy in resected primary melanoma thicker than 1.5 mm without clinically detectable node metastases. French Cooperative Group on Melanoma. Lancet 1998;351:1905-10.

[6] Eggermont AM, Suciu S, Santinami M, Testori A, Kruit WH, Marsden J, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. Lancet 2008;372:117-26.

[7] Wheatley K, Ives NJ, Hancock B, Gore M, Eggermont A, Suciu S. Does adjuvant interferon-α for high-risk melanoma provide a worthwhile benefit? A meta-analysis of the randomised trials. Cancer Treat Rev 2003;29:241-52.

[8] Wheatley K, Ives N, Eggermont A, Kirkwood J, Cascinelli N, Markovic SN, et al. Interferon-α as adjuvant therapy for melanoma: An individual patient data meta-analysis of randomised trials. J Clin Oncol 2007;25 (Suppl) [Abstract 8526]

[9] Mocellin S, Lens MB, Pasquali S, Pilati P, Chiarion Sileni V. Interferon alpha for the adjuvant treatment of cutaneous melanoma. Cochrane Database Syst Rev. 2013 Jun 18;6:CD008955. doi: 10.1002/14651858.CD008955.pub2.

[10] Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27:6199-206.

[11] Stewart LA, Clarke MJ. Practical methodology of meta-analyses (overviews) using updated individual patient data. Cochrane Working Group. Stat Med 1995;14:2057-79.

[12] Early Breast Cancer Trialists' Collaborative Group. Treatment of Early Breast Cancer. Vol 1: Worldwide evidence 1985-1990. Oxford University Press, Oxford 1990.

[13] Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815-34.

[14] Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al: PRISMA-IPD Development Group. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA 2015;313:1657-65.

[15] Eggermont AM, Suciu S, MacKie R, Ruka W, Testori A, Kruit W, et al. EORTC Melanoma Group. Post-surgery adjuvant therapy with intermediate doses of interferon alfa 2b versus observation in patients with stage IIb/III melanoma (EORTC 18952): randomised controlled trial. Lancet 2005;366:1189-96.

[16] Creagan ET, Dalton RJ, Ahmann DL, Jung SH, Morton RF, Langdon RM Jr, et al. Randomized, surgical adjuvant clinical trial of recombinant interferon alfa-2a in selected patients with malignant melanoma. J Clin Oncol 1995;13:2776-83.

[17] McMasters KM, Ross MI, Reintgen DS, et al. Final results of the Sunbelt Melanoma Trial. J Clin Oncol 2008:26 (Suppl) [Abstract 9003]

[18] Hansson J, Aamdal S, Bastholt L, Brandberg Y, Hernberg M, Nilsson B, et al. Two different durations of adjuvant therapy with intermediate-dose interferon alfa-2b in patients with high-risk melanoma (Nordic IFN trial): a randomised phase 3 trial. Lancet Oncol 2011;12:144–52.

[19] Cascinelli N, Belli F, MacKie RM, Santinami M, Bufalino R, Morabito A. Effect of long-term adjuvant therapy with interferon alpha-2a in patients with regional node metastases from cutaneous melanoma: a randomised trial. Lancet 2001;358:866-9.

[20] Hancock BW, Wheatley K, Harris S, Ives N, Harrison G, Horsman JM, et al. Adjuvant interferon in high-risk melanoma: the AIM HIGH Study - United Kingdom Coordinating Committee on Cancer Research randomized study of adjuvant low-dose extended-duration interferon Alfa-2a in high-risk resected malignant melanoma. J Clin Oncol 2004;22:53-61.

[21] Garbe C, Radny P, Linse R, Dummer R, Gutzmer R, Ulrich J, et al. Adjuvant low-dose interferon alpha-2a with or without dacarbazine compared with surgery alone: a prospective-randomized phase III DeCOG trial in melanoma patients with regional lymph node metastasis. Ann Oncol 2008;19:1195-201.

[22] Pehamberger H, Soyer HP, Steiner A, Kofler R, Binder M, Mischer P, et al. Adjuvant interferon alfa-2a treatment in resected primary stage II cutaneous melanoma. Austrian Malignant Melanoma Cooperative Group. J Clin Oncol 1998;16:1425-29.

[23] Cameron DA, Cornbleet MC, MacKie RM, Hunter JA, Gore M, Hancock B, et al. Adjuvant interferon alpha 2b in high risk melanoma - the Scottish study. Br J Cancer 2001;84:1146-49.

[24] Kleeberg UR, Suciu S, Brocker EB, Ruiter DJ, Chartier C, Lienard D, et al. EORTC Melanoma Group in cooperation with the German Cancer Society (DKG). Final results of the EORTC 18871/DKG 80-1 randomised phase III trial: rIFN-alpha2b versus rIFN-gamma versus ISCADOR M versus observation after surgery in melanoma patients with either high-risk primary (thickness >3 mm) or regional lymph node metastasis. Eur J Cancer 2004;40:390-402.

[25] Kirkwood JM, Ibrahim JG, Sosman JA, Sondak VK, Agarwala SS, Ernstoff MS, et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. J Clin Oncol 2001;19:2370-80.

[26] Kirkwood JM, Ibrahim J, Lawson DH, Atkins MB, Agarwala SS, Collins K, et al. High-dose interferon alfa-2b does not diminish antibody response to GM2 vaccination in patients with resected melanoma: results of the Multicenter Eastern Cooperative Oncology Group Phase II Trial E2696. J Clin Oncol 2001;19:1430-6.

[27] Eggermont AM, Suciu S, Testori A, Kruit WH, Marsden J, Punt CJ, et al. Ulceration and stage are predictive of interferon efficacy in melanoma: results of the phase III adjuvant trials EORTC 18952 and EORTC 18991. Eur J Cancer 2012;48:218-25.

[28] Eggermont AM, Spatz A, Robert C. Cutaneous melanoma. Lancet 2014;383:816-27.

[29] Eggermont AM, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, Schmidt H, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III

melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol 2015;16:522-30.

Acknowledgements

We would like to thank all the patients who participated in the trials of adjuvant interferon for melanoma included in this meta-analysis. We thank Professor Robert K. Hills for his help in creating the database that performed all the analyses.

Funding

No funders were directly involved in the project. This work was supported by the University of Birmingham Clinical Trials Unit who received core support from the UK Department of Health, through the National Co-ordinating Centre for Research Capacity Development, up to March 2012, which funded Natalie Ives. A core grant from the Fonds Cancer, FOCA (BE), provides support for the EORTC Headquarters staff (co-author, Stefan Suciu).

The following groups (listed alphabetically, with the names of investigators/ statisticians as nominated by each group) supplied individual patient data for the overview: *ECOG, USA:* John Kirkwood, Sandra Lee; *EORTC:* Alexander Eggermont, Stefan Suciu; *DeCOG*: Claus Garbe, Michael Kressig; *NCCTG:* Svetomir N. Markovic, Vera Suman; *Scottish MG:* David Cameron, Valerie Doherty, Rona Mackie; *UK-CCCR AIM-High:* Paul Lorigan, Barry Hancock, Lesley Turner; *WHO 16 Melanoma Group:* Natale Cascinelli (deceased), Rosaria Bufalino.

Additional published data were provided by: *Sunbelt*: Kelly McMasters.

Members of The International Melanoma Meta-Analysis Collaborative Group: Rosaria Bufalino, David Cameron, Natale Cascinelli (deceased), Valerie Doherty, Alexander Eggermont, Claus Garbe, Martin Gore, Barry Hancock, Rebecca Harrison, Natalie Ives,

John Kirkwood, Michael Kressig, Sandra Lee, Paul Lorigan, Rona MacKie, Svetomir N. Markovic, Jerry Marsden, Stefan Suciu, Vera Suman, Lesley Turner, Keith Wheatley.

Writing Committee: Natalie Ives, Stefan Suciu, Alexander Eggermont, John Kirkwood, Paul Lorigan, Svetomir N. Markovic, Claus Garbe, Keith Wheatley.

We, the members of writing committee on behalf of the International Melanoma Meta-Analysis Collaborative Group, declare that we participated in the design, analysis and interpretation of this research, and that we have seen and approved the final version.

Author Contributions:

NI developed and designed the project, wrote the protocol and data requirement documents, undertook all the statistical analyses, interpreted the analyses and wrote the manuscript.

SS designed the project and was involved in the protocol development. SS also provided individual patient data from the EORTC trials, interpreted the analyses and reviewed and commented on the manuscript.

AE designed the project and was involved in the protocol development. AE also provided individual patient data from the EORTC trials, interpreted the analyses and reviewed and commented on the manuscript.

JK designed the project and was involved in the protocol development. JK also provided individual patient data from the ECOG trials, interpreted the analyses and reviewed and commented on the manuscript.

PL was involved in the protocol development, and was the investigator representing the AIM-HIGH trial for which individual patient data was provided. PL interpreted the analyses and reviewed and commented on the manuscript.

SM provided individual patient data from the NCCTG 83-7052 trial. SM interpreted the analyses and reviewed and commented on the manuscript.

CG provided individual patient data from the DeCOG trial. CG interpreted the analyses and reviewed and commented on the manuscript.

KW devised and developed the project. KW was involved in the protocol development, supervised the analyses, interpreted the analyses and reviewed and commented on the manuscript.

Table 1: Trial Design and Number of Patients Randomised into Trials of Adjuvant Interferon-α Therapy versus Control for High-Risk Melanoma

Trial	Comparison	Dose Schedule	Duration of Treatment	Total Planned Dose (MU)	Number of Patients Randomised	Number of Patients Analysed	Median Duration of Follow-Up (Range)
Trials of IFN vs. No IFN							
ECOG 1684	High Dose IFNα-2b versus Observation	20 MU/m^2/d IV 5 days per week for 4 weeks. Then 3 times weekly at 10 MU/m^2/d SC for 48 weeks.	1 year	3500	N = 287 IFN = 146 Obs = 141	N = 287 IFN = 146 Obs = 141	16.9 years in 93 survivors (0 – 19.9 years)
ECOG 1690	High and Low Dose IFNα-2b versus Observation (3 arm trial)	High Dose: 20 MU/m^2/d IV 5 days per week for 4 weeks. Then 3 times weekly at 10 MU/m^2/d SC for 48 weeks. Low Dose: 3 MU/d SC 3 times week for 2 years.	1 year 2 years	3500 936	N = 642 High = 215 Low = 215 Obs = 212	N = 642 High = 215 Low = 215 Obs = 212	10.7 years in 294 survivors (0.8 – 13.9 years)
NCCTG 83-7052	High Dose IFNα-2a versus Observation	20 MU/m^2/d IV 3 times weekly for 12 weeks.	3 months	1350	N = 264 IFN = 132 Obs = 132	N = 264 IFN = 132 Obs = 132	15.1 years in 98 survivors (6.2 – 18.9 years)
Sunbelt	High Dose IFNα-2b versus Observation	20 MU/m^2/d IV 5 days per week for 4 weeks. Then 3 times weekly at 10 MU/m^2/d SC for 48 weeks.	1 year	3500	N = 218 IFN = 112 Obs = 106	N = 218 IFN = 112 Obs = 106	64 months (from abstract)
EORTC 18952	Intermediate Dose IFNα-2b versus	IFN Arm 1: 10 MU SC 5 times weekly for 4 weeks. Then 10 MU SC 3 times weekly for 1 year.	13 months	1760	N = 1418† 1 year = 565	N = 1388 1 year = 553	4.6 years in 707 survivors

	Observation (3 arm trial)	IFN Arm 2: 10 MU SC 5 times weekly for 4 weeks. Then 5 MU SC 3 times weekly for 2 years. CONTINUE treatment in case of regional relapse until DISTANT relapse or completion of schedule.	25 months	1760	2 years = 569 Obs = 284	2 years = 556 Obs = 279	(0.08 – 7 years)
Nordic	Intermediate Dose IFNα-2b versus Observation (3 arm trial)	IFN Arm 1: 10 MU SC 5 times weekly for 4 weeks. Then 10 MU SC 3 times weekly for 1 year. IFN Arm 2: 10 MU SC 5 times weekly for 4 weeks. Then 10 MU SC 3 times weekly for 2 years.	13 months 25 months	1760 3320	N = 855 1 year = 285 2 years = 286 Obs = 284	N = 855 1 year = 285 2 years = 286 Obs = 284	72.4 months (from paper)
WHO 16	Low Dose IFNα-2a versus Observation	3 MU SC 3 times weekly for 3 years.	3 years	1400	N = 444 IFN = 225 Obs = 219	N = 444 IFN = 225 Obs = 219	6.1 years in 165 survivors (0 – 8.9 years)
UKCCCR AIM-High	Low Dose IFNα-2a versus Observation	3 MU SC 3 times weekly for 2 years.	2 years	936	N = 674 IFN = 338 Obs = 336	N = 674 IFN = 338 Obs = 336	5.5 years in 287 survivors (0 – 9.3 years)
DeCOG	Low Dose IFNα-2a versus Observation	3 MU SC 3 times weekly for 2 years.	2 years	936	N = 296†† IFN = 148 Obs = 148	N = 293 IFN = 146 Obs = 147	3.9 years in 140 survivors (0.5 – 6.9 years)
French CGM	Low Dose IFNα-2a versus Observation	3 MU SC 3 times weekly for 18 months.	18 months	702	N = 499††† IFN = 253 Obs = 246	N = 489 IFN = 244 Obs = 245	5 years (from publication)

Austrian MMCG	Low Dose IFNα-2a versus Observation	3 MU SC daily for 3 weeks then 3 MU SC 3 times weeks for 49 weeks.	1 year	513	N = 311 IFN = 154 Obs = 157	N = 311 IFN = 154 Obs = 157	Mean = 41 months (from publication)
Scottish MG	Low Dose IFNα-2b versus Observation	3 MU SC 3 times weekly for 6 months.	6 months	234	N = 96†††† IFN = 47 Obs = 49	N = 94 IFN = 46 Obs = 48	6.5 years in 28 survivors (0.5 – 9.8 years)
EORTC 18871	Low Dose IFNα-2b versus Observation	1 MU SC on alternate days for 1 year.	1 year	182	N = 281 IFN = 139 Obs = 142	N = 281 IFN = 139 Obs = 142	7.8 years in 105 survivors (0 – 14 years)
DKG 80-1	Very Low Dose IFNα-2b versus Observation	1 MU SC on alternate days for 1 year.	1 year	182	N = 203 IFN = 101 Obs = 102	N = 203 IFN = 101 Obs = 102	7.2 years in 94 survivors (0 – 13.3 years)
Trial of PEG-IFN vs. No PEG-IFN							
EORTC 18991	PEG-IFN versus Observation	6 µg/kg/wk SC for 8 weeks. Then 3 µg/kg/wk SC for 5 years.	5 years	-	N = 1256 IFN = 627 Obs = 629	N = 1256 IFN = 627 Obs = 629	7.54 years in 588 survivors (0.3 – 10.3 years)
Vaccine Trials							
ECOG 2696	High Dose IFNα-2b and GM2-KLH/QS-21 vaccine (IFN either	20 MU/m^2/d IV 5 days per week for 4 weeks. Then 3 times weekly at 10 MU/m^2/d SC for 48 weeks.	1 year	3500	N = 107 IFN = 72 Obs = 35	N = 107 IFN = 72 Obs = 35	7.1 years in 55 survivors (1.4 – 8.1 years)

	started on same day as vaccine or deferred until day 28) versus GM2-KLH/QS-21						
ECOG 1694	High Dose IFNα-2b versus GMK vaccine	IFN: 20 MU/m2/d IV 5 days per week for 4 weeks. Then 3 times weekly at 10 MU/m2/d SC for 48 weeks. GMK vaccine: 1 mL of GMK vaccine administered via a deep SC injection on days 1, 8, 15, and 22, then every 12 weeks (weeks 12 to 96).	1 year 2 years	3500	N = 880 IFN = 440 GMK = 440	N = 880 IFN = 440 GMK = 440	5.9 years in 472 survivors (0 – 8.5 years)

† In the EORTC 18952 trial, 1418 patients were randomised, but 30 patients (all from one centre) were excluded because of concerns about data quality.

†† In the DeCOG trial, 3 patients were excluded from the intention to treat analysis due to having stage IV melanoma (n=2) or another type of malignancy (n=1).

††† In the French CGM trial, 10 patients were excluded from the intention to treat analysis due to being ineligible (n=5) or immediate withdrawal of consent (n=5).

†††† In the Scottish MG trial, 2 patients were excluded from the intention to treat analysis due to being ineligible (n=1) or lost to follow (n=1).